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JACC GUIDELINE COMPARISON

International Clinical Practice Guideline Recommendations for Acute Pulmonary Embolism

Harmony, Dissonance, and Silence

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ABSTRACT

Despite abundant clinical innovation and burgeoning scientific investigation, pulmonary embolism (PE) has continued to pose a diagnostic and management challenge worldwide. Aging populations, patients living with a mounting number of chronic medical conditions, particularly cancer, and increasingly prevalent health care disparities herald a growing burden of PE. In the meantime, navigating expanding strategies for immediate and long-term anticoagulation, as well as advanced therapies, including catheter-based interventions for patients with more severe PE, has become progressively daunting. Accordingly, clinicians frequently turn to evidence-based clinical practice guidelines for diagnostic and management recommendations. However, numerous international guidelines, heterogeneity in recommendations, as well as areas of uncertainty or omission may leave the readers and clinicians without a clear management pathway. In this review of international PE guidelines, we highlight key areas of consistency, difference, and lack of recommendations (silence) with an emphasis on critical clinical and research needs. (JACC. 2024;84:1561–1577) © 2024 by the American College of Cardiology Foundation.

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SHOUT
SHARE
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ABBREVIATIONS AND ACRONYMS

ASH = American Society of Hematology

CDI = catheter-directed intervention

CTEPH = chronic thromboembolic pulmonary hypertension

CTPA = computed tomography pulmonary angiography

DOAC = direct oral anticoagulant

IVC = inferior vena cava

LMWH = low-molecular-weight-heparin

NICE = National Institute for Health and Care Excellence

PE = pulmonary embolism

PERT = Pulmonary Embolism Response Team

PESI = Pulmonary Embolism Severity Index

RCT = randomized controlled trial

RV = right ventricular

TTE = transthoracic echocardiography

UFH = unfractionated heparin

VKA = vitamin K antagonist

V/Q = ventilation/perfusion lung scan

VTE = venous thromboembolism

Despite abundant clinical practice innovation and burgeoning scientific investigation, acute pulmonary embolism (PE) still poses a major diagnostic and management challenge worldwide. Aging populations comprised of patients living with a mounting number of chronic medical conditions that predispose to venous thromboembolism (VTE), such as cancer, obesity, and cardiovascular disease, portend a growing global burden of PE. Climbing annual incidence rates for PE from 1997 to 2013 in the United States, Europe, and Australia have confirmed such a prediction.[1,2] Although overall case fatality and mortality rates have declined in the United States and Europe, the number of deaths appears to be increasing in key subpopulations, including young and middle-aged adults and those with more severe presentations.[3-6]

Evidence-based clinical practice guidelines serve a critical role in standardizing care for patients with PE and help guide clinicians by providing comprehensive management recommendations.[7] However, as with other areas of cardiovascular medicine, heterogeneity in the clinical care of patients with PE, especially as related to social determinants of health, runs counter to this effort.[8,9] Further complicating the care of patients with PE is the rapidly expanding number of interventional options, including catheter-based therapies and mechanical circulatory support devices, many with only limited evidence of efficacy and safety from randomized trials.[10] Inadequate data for integration of device therapy for PE as well as other key aspects of management, such as lifestyle modification and follow-up for short- and long-term complications, hamper the ability of guideline writing committees to provide clear or consistent recommendations. The multiplicity of guidelines, scientific statements, and standardization documents as well as numerous areas of disagreement and inconsistency in recommendations may leave the clinician without a clear management pathway.

In this review, we highlight key areas of consistency, difference, and lack of recommendation between North American and European evidence-based clinical practice guidelines for PE, scientific statements, and standardization documents, with an emphasis on critical clinical and research needs and pathways forward.

METHODOLOGY

For consideration of professional society recommendations (hereafter referred to as *guidelines*), we focused on those that were published in English language from European or North American societies and were based on systematic evidence review (ie, predefined and preferentially reproducible search criteria) and evidence synthesis (such as those of Grading of Recommendations Assessment, Development and Evaluation [GRADE] criteria[11]).

Certain professional societies provided summary documents related to PE without systematic review and critiquing of evidence. Although many such documents have value based on expert input, such documents often lack reproducible processes and are comparable to expert narrative review papers. It was prespecified to refer to such documents on a case-by-case basis, but not to include them in the main summary figures for diagnosis, prognosis, or management recommendations. Recognizing that guidelines are meant to provide evidence summary and general guidance rather than individualized care for every patient, a summary of guidelines, as provided herein, is also meant to provide general recommendations for daily clinical practice. Although there are many patient groups that may require special considerations surrounding the diagnosis and management of PE, we elected to highlight specific guidance for 2 common and clinically challenging populations: patients with pregnancy and those with cancer. These subgroups of patients were selected for their epidemiological importance and impact on prognosis.

In the present review, the professional society documents, in English language, were primarily selected based on consensus between the co-lead authors (M.Z. and B.B.) and the senior author (G.P.), in discussion with coauthors. A search of PubMed was performed to ensure that no potentially relevant guideline was missed ("Pulmonary Embolism"[MAJR] OR pulmonary*[TI] AND [embolism*(TI) OR thromboembo*(TI)] AND guideline*[TI], date last searched: December 31, 2023). Differences and disagreements in opinion were addressed through meetings and electronic communications. Areas of uncertainty were also noted with the hopes that future basic and clinical research will advance knowledge in this field.

The guidelines identified for this review were authored by the European Society of Cardiology and European Respiratory Society (ESC/ERS),[2] Pulmonary Embolism Response Team Consortium (PERT),[12]

FIGURE 1 Summary of Professional Society Recommendations About Diagnosis of Acute PE

✓ Suggested ⚠ Not Addressed ✗ Not Recommended	ESC/ERS[2]	PERT[12]	CHEST[13]	AHA[14]	ASH[15]	NICE[20]
Assessment of pretest probability	✓ a	✓	⚠	✓ a	✓	✓ f
Use of D-dimer in patients with low or intermediate pretest probability of PE	✓	✓	⚠	⚠	✓	✓
Use of age-adjusted or probability-adjusted D-Dimer in patients with low or intermediate pretest probability of PE	✓	✓	⚠	⚠	✓ g	✓ g
Use of D-dimer in patients with a high pretest probability of PE	✗	✗	⚠	⚠	✓	✗
Use of the Pulmonary Embolism Rule-out Criteria (PERC)	⚠	✓ b	⚠	⚠	✓ b	✓
Use of CTPA as initial imaging modality	✓ c	✓ d	⚠	⚠	✓ e	✓
Use of V/Q lung scan as initial imaging modality	⚠	✓ d	⚠	⚠	✓	✓
Diagnostic approaches in pregnancy	✓ h	⚠	⚠	⚠	✓ i	⚠

a. Assessment using either clinical judgment and/or a validated clinical prediction rule, such as the Wells[22] or the Geneva scores[23].
b. PERT recommends the use of PERC in patients with a low pretest PE probability based on another validated tool (such as Wells or Geneva)[22,23].
c. ESC/ERS offers further recommendations based upon the results of the CTPA. They also offer recommendations for alternative imaging strategies that may be utilized.
d. PERT makes a specific recommendation for the use of portable V/Q scanning or echocardiography in cases where CTPA is contraindicated or not available.
e. ASH guidelines recommend the use of CTPA when V/Q scan is not feasible.
f. NICE recommends the two-level Wells Score.
g. ASH and NICE recommend age-adjusted d-Dimer in patients >50 years
h. ESC/ERS comments on the approach to PE in pregnancy.
i. ASH provides specific comments regarding the approach to PE in pregnancy into a dedicated guideline[19].

AHA = American Heart Association; ASH = American Society of Hematology; CTPA = computed tomography pulmonary angiography; ERS European Society of Cardiology; ESC = European Society of Cardiology; NICE = National Institute for Health and Care Excellence; PE = pulmonary embolism; PERT = Pulmonary Embolism Response Team; V/Q = ventilation/perfusion lung scan.

CHEST (previously referred to as the American College of Chest Physicians guidelines),[13] the American Heart Association (AHA),[14] the American Society of Hematology (ASH),[15-19] and the National Institute for Health and Care Excellence (NICE).[20,21] Some professional societies provided all recommendations in one document, and others published them in multiple documents. If the latter was the case for any given question, the reference was to the most updated document that followed the eligibility criteria. In addition to summarizing those guidelines, at the conclusion of each section, practical considerations are offered by the current author group. Of note, differences in guideline recommendations are likely multifactorial, and are partly driven by the time of publication (and evidence review) or regional variation in resource availability and treatment strategies.

DIAGNOSIS OF ACUTE PE

The need for early diagnosis is emphasized by multiple societal guidelines[2,12,15,20] (**Figure 1**). ESC/ERS, NICE, ASH, and PERT guidelines propose utilization

of stepwise diagnostic algorithms.[2,12,15,20] Most current guidelines emphasize initial patient assessment using validated pretest probability scores, with different preferences between documents for tools such as the Wells' or the Geneva score.[22,23] Furthermore, all recommend D-dimer testing to exclude acute PE in case of non-high-pretest probability; ESC/ERS[2] and PERT[12] suggest using age-adjusted[24] or probability-adapted[25] cutoffs, whereas NICE[20] and ASH[15] suggest the use of age-adjusted cutoffs in patients over 50 years of age. ASH,[15] NICE,[20] and PERT[12] suggest the use of the Pulmonary Embolism Rule-out Criteria (PERC)[26] in patients felt to have a low pretest probability of PE, allowing the identification of a patient subgroup in whom no further testing is indicated. The ESC/ERS[2] does not incorporate the Pulmonary Embolism Rule-out Criteria,[26] noting that the evidence for its use is still limited and may be unsafe to rule out acute PE in settings with an expected higher prevalence of PE.

Much like routine practice, there is variation across guidelines for the imaging modality of choice.[27] ESC/ERS,[2] NICE,[20] and PERT[12] highlight that computed tomographic pulmonary angiography (CTPA) is the primary diagnostic imaging tool for acute PE. In contrast, the ASH guidelines recommend the use of ventilation/perfusion (V/Q) lung scan over CTPA to limit radiation exposure, in centers able to perform studies rapidly and with the expertise to interpret the results in a timely manner.[15] The use of CTPA is suggested when V/Q scanning and review by experts are not feasible.[15] Both the ESC/ERS[2] and PERT[12] documents suggest the use of transthoracic echocardiography (TTE), V/Q lung scintigraphy, or pulmonary angiography, when available, in case of contraindications or inability to obtain CTPA. Furthermore, in patients with clinical deterioration and suspected PE, the ESC/ERS guidelines recommend bedside echocardiography or emergency CTPA, depending on availability and clinical circumstances, for diagnosis and prognostication.[2] Additionally, the ESC/ERS guidelines[2] suggest the use of compression ultrasound of the lower limbs as a diagnostic tool in patients who have signs or symptoms of PE but cannot undergo chest imaging for PE. Other professional societies are silent on this approach.

During pregnancy, the ESC/ERS guidelines assert that the diagnosis of PE should be further considered in the presence of a high pretest probability (Geneva score) or intermediate/low probability with a positive unadjusted D-dimer result.[2] In this context, a chest x-ray may be the first imaging test.[2] Moreover, according to these guidelines, CTPA, employing a low-dose radiation protocol, is recommended as the primary imaging approach to rule out PE in this population, especially if the chest x-ray is abnormal, such that the accuracy of a V/Q scan may be negatively impacted.[2] Because D-dimer levels are often elevated in pregnancy, particularly in the third trimester, the usual cutoff level is not suitable during pregnancy or the perinatal period. Instead, the ESC/ERS guidelines[2] suggest that the use of customized strategies, such as the modified YEARS algorithm, may limit unnecessary CTPAs.[28] A separate ASH guideline addresses VTE in the context of pregnancy, with a single recommendation for the use of V/Q scanning as the primary imaging modality.[19] None of the societies specifically address diagnostic strategies in patients with cancer.

PRACTICAL CONSIDERATIONS. Suspicion of PE should be assessed using a validated pretest probability score. In patients with low pretest probability, a negative D-dimer result excludes the diagnosis of PE, whereas a positive test or a high initial pretest probability must be followed by imaging. The diagnostic imaging test of choice should be the one that is most readily available and reliable at a particular site. Due to the widespread availability of CT and diminishing expertise with V/Q scanning at many centers, CTPA is frequently the modality of choice.

RISK STRATIFICATION

Once the diagnosis of acute PE is objectively confirmed, determining the severity of illness, assessing prognosis, and synthesizing such information to risk-stratify patients with PE play critical roles.[29,30] Risk stratification can assist physicians in selecting the location of care (home, general medical wards, intermediate care unit, or intensive care unit) and the optimal treatment (ie, whether advanced therapies should be considered).

There is heterogeneity in international guidelines with respect to grading of PE severity and recommended prognostication tools. Five guidelines[2,12-15] provided recommendations for identification of high-risk (massive) PE and acknowledged that this subgroup should be defined as sustained hypotension (systolic blood pressure $<$90 mm Hg[2,12-14,16] or a decrease in systolic blood pressure $\geq$40 mm Hg from baseline[2,12,14,16] or need for vasopressor support[2,14]). Although the AHA[14] guidelines identify low-risk PE patients as those who are hemodynamically stable and without evidence of right ventricular (RV) strain, that document was published earlier than the others and did not address the incorporation of prognostic scores. Guideline documents vary in their approach to the definition of RV dysfunction based on imaging.

The 2019 ESC/ERS guidelines emphasize a comprehensive echocardiographic assessment, with parameters such as an RV/left ventricular (LV) diameter ratio of >1.0 and tricuspid annular plane systolic excursion (TAPSE) <16 mm consistent with RV dysfunction.[2] Based on CTPA assessment, the 2019 ESC/ERS guidelines state that an RV/LV diameter ratio of at least 1.0 is consistent with RV dysfunction.[2] The 2011 AHA scientific statement defines RV dysfunction on imaging as an RV/LV diameter ratio of >0.9 or RV systolic dysfunction on echocardiography or an RV/LV diameter ratio of >0.9 on CTPA.[14] The PERT document endorses assessment of RV dysfunction via echocardiography or CTPA but does not provide specific definitions.[12] The CHEST, ASH, and NICE documents do not provide specific recommendations for assessment and definition of RV dysfunction.[13,15,20]

The use of a validated prognostic score, such as the Pulmonary Embolism Severity Index (PESI)[31] or its simplified version,[29,32] is endorsed by guidelines from ESC/ERS,[2] PERT,[12] and ASH.[16] The PESI score is based on 11 differently weighted variables, allowing the identification of patients at low risk for 30-day mortality (PESI classes I and II).[31] However, because of the complexity of the PESI, a simplified version, evaluating age, history of cancer, history of chronic cardiopulmonary disease, heart rate, systolic blood pressure, and oxyhemoglobin saturation level, is often used to identify patients at low risk for 30-day mortality.[32] ESC/ERS[2] and CHEST[13] guidelines also suggest an assessment of the RV size and function for the identification of low-risk patients with acute PE. Only 4 guidelines (ESC/ERS,[2] PERT,[12] AHA,[14] and ASH[15]) provide guidance on how to identify hemodynamically stable patients with intermediate-risk (submassive) PE. Although AHA[14] and ASH[15] recommend diagnosing intermediate-risk PE when RV dysfunction or strain are detected, the ESC/ERS[2] and PERT[12] guidelines further subdivide this group into an intermediate-low risk and an intermediate-high risk category, requiring both RV dysfunction on imaging and elevation of at least 1 biomarker, typically conventional cardiac troponin.[33] In a recent study, comparing high-sensitivity and conventional care troponin I, high-sensitivity troponin I identified additional patients as having a "positive" troponin but did not improve the identification of patients who suffered from adverse events[33] (**Figure 2**).

An elevation of markers of RV dysfunction, such as B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide may provide additional prognostic information. However, these markers have not yet been used to guide treatment decisions in randomized controlled trials.[2]

PRACTICAL CONSIDERATIONS. Risk stratification synthesizing an assessment of clinical severity, cardiac biomarkers, and imaging evidence of RV dysfunction is a critical component of the evaluation of patients with PE.

TRIAGE OF PE AND LEVEL OF CARE

A recent shift toward home-based care and early discharge for low-risk acute PE patients is supported by the ESC/ERS,[2] CHEST,[13] NICE,[20] and ASH[16] guidelines. ESC/ERS[2] and ASH[16] offer specific patient selection criteria, suggesting the use of clinical scores. ESC/ERS[2] suggest the use of PESI or simplified PESI rules[31,32] (or, alternatively, the Hestia criteria[34]) for clinical triage. Specifically, in the absence of abnormal RV imaging on echocardiography or CTPA and with a favorable PESI/simplified PESI/Hestia[31,32,34] score, the feasibility of early discharge and home treatment must be considered. The CHEST guidelines[13] address practical home care aspects such as the use of direct oral anticoagulants (DOACs). The recent HOME-PE study[35] has confirmed the safety and feasibility of home treatment of PE patients selected with either simplified PESI or Hestia criteria.[32] All documents emphasize the importance of adequate access to follow-up health care and patient commitment to medication adherence. The AHA 2011 statement[14] excludes discussion of home-based care, focusing on more severe PE cases.

Multidisciplinary pulmonary embolism response teams (PERTs)[12] are now considered integral components of PE care at many institutions and guide early management decisions, particularly in patients with more severe presentations. Of the guideline documents, only ESC/ERS[2] and PERT[12] advocate for their role, recommending consideration of establishing PERTs when resources permit. There is heterogeneity regarding which specialties comprise a multidisciplinary PE response team from one institution to another. Although guidelines recommend inclusive multidisciplinary team care for PE, documents do not specify which subspecialties are required. Additionally, the ESC/ERS[2] and PERT[12] guidelines highlight the role of team-based care in clinical decision-making for reperfusion therapy. Although ASH[16] acknowledges the growing use of PERTs, it recognizes the lack of high-quality evidence demonstrating improved outcomes in PE patients and thus does not provide a specific recommendation (**Figure 2**).

PRACTICAL CONSIDERATIONS. Home-based care is encouraged in patients with low-risk PE, reliable

FIGURE 2 Recommendations for Risk Stratification, Home-Based Care, and the Use of Multidisciplinary Response Teams for Acute PE Across Guideline Documents

✓ Suggested ⚠ Not Addressed ✗ Not Recommended	ESC/ERS[2]	PERT[12]	CHEST[13]	AHA[14]	ASH[15]	NICE[20]
Recommendation for risk stratification	✓	✓	⚠ a	✓	⚠	⚠
Definition provided for low-risk PE	✓	✓	✓	✓	✓	⚠
Definition provided for intermediate-risk (submassive) PE	✓	✓	⚠	✓	✓	⚠
Definition provided for intermediate-low risk PE	✓	✓	⚠	⚠	⚠	⚠
Definition provided for intermediate-high risk PE	✓	✓	⚠	⚠	⚠	⚠
Definition provided for PE deterioration	⚠	✓	✓	⚠	⚠	⚠
Definition provided for high-risk (massive) PE	✓	✓	✓	✓	✓	⚠
Early discharge or entirely home-based care for low-risk PE	✓ c	✓	✓	⚠ b	✓	✓
Use of a multidisciplinary PERT	✓	✓	⚠	⚠ b	⚠ d	✓

a. While the CHEST guidelines focused on antithrombotic therapy for VTE, the general concept of risk stratification is discussed in the document.
b. The AHA Statement does not address home-based care. It also predated the development of PERTs and does not address the use of PERTs.
c. The ESC/ERS also considers whether assessment of right ventricular function, in addition to the clinic assessment, is necessary prior to sending patients home. Though not part of the recommendation, the authors note that given "the ease and minimal additional effort of assessing RV size and function at presentation by echocardiography, or on the CTPA performed to diagnose the PE event itself, it is wise to exclude RV dysfunction and right heart thrombi if immediate or early (within the first 24-48h) discharge of the patient is planned."
d. The use of PERT is addressed but without specific recommendation based on lack of data.

Abbreviations as in Figure 1.

medication adherence, and adequate health care support. Multidisciplinary PE response teams are recommended, based on consensus opinion, in the context of limited high-quality evidence indicative of improved outcomes.

IMMEDIATE ANTICOAGULATION

In patients with suspected PE, there is consensus across professional societies to consider empiric therapeutic anticoagulation while awaiting the results of confirmatory tests in patients with intermediate or high pretest probability of PE, provided that the risk of bleeding is low[2,14,20] (**Figure 3**). In patients with confirmed PE, therapeutic anticoagulation is the cornerstone of treatment. The choice of anticoagulant differs depending on the severity of the PE. The ESC/ERS[2] guidelines recommend anticoagulation with unfractionated heparin (UFH), including a weight-adjusted bolus injection, as soon as possible, in patients with suspected high-risk PE. Similarly, the ESC/ERS,[2] PERT,[12] and NICE[20] guidelines recommend UFH for hemodynamically unstable PE if advanced therapies such as thrombus extraction, fibrinolysis, or surgery are being considered. UFH is frequently utilized in high-risk and intermediate high-risk PE to minimize periprocedural bleeding when administering advanced therapies, such as systemic fibrinolysis or catheter-based intervention. However, most patients fail to achieve and consistently maintain therapeutic activated partial thromboplastin times within the first 48 hours after diagnosis with standard UFH dosing nomograms.[36] Due to the concern of subtherapeutic or supratherapeutic anticoagulation

FIGURE 3 Professional Society Recommendations for Immediate Anticoagulation for Acute PE

✓ Suggested ⚠ Not Addressed ✗ Not Recommended	ESC/ERS[2]	PERT[12]	CHEST[13]	AHA[14]	ASH[16]	NICE[20]
Therapeutic anticoagulation should be initiated while awaiting diagnostic results if the pretest probability of PE is intermediate or high and the bleeding risk is low	✓	✓	⚠	✓	⚠	✓ a
Therapeutic anticoagulation should be given to all patients with confirmed PE who do not have a contraindication	✓	✓	✓	✓ b	✓	✓
Immediate anticoagulant choice in high-risk PE if advanced therapies are considered: unfractionated heparin	✓	✓	⚠	⚠	⚠	✓
Immediate anticoagulant in intermediate-high risk PE not requiring advanced therapies: LMWH or DOAC (unless contraindications)	✓	⚠	⚠	⚠	✓ c	✓
Immediate anticoagulant choice in low-risk PE: DOAC (unless contraindications)	✓ d	✓	⚠	⚠	✓ c	✓
Immediate anticoagulant choice in patients with HIT or a history of HIT: parenteral direct thrombin inhibitor or fondaparinux	✓ e	⚠	⚠	✓ f	✓ g	⚠
For oral anticoagulation in the treatment phase of PE, DOAC is recommended over VKA unless there is severe kidney disease, concomitant use of interacting drugs, or antiphospholipid syndrome	✓ f	✓	✓	⚠	✓	✓

a. If PE unlikely, but D-dimer cannot be offered within 4 hours, NICE 2020 guidelines recommend interim anticoagulation while awaiting results.
b. Therapeutic anticoagulation with LMWH, IV/SC heparin, or fondaparinux is recommended for all patients with confirmed PE.
c. ASH does not differentiate the choice of agents based on acuity of care.
d. For immediate treatment with DOACs, apixaban and rivaroxaban can start immediately, whereas edoxaban and dabigatran need a short course of initial treatment with heparin-based regimens.
e. No preference for parenteral or oral anticoagulation for intermediate or low-risk PE in the formal recommendations; LMWH or fondaparinux preferred over UFH.
f. AHA recommends danaparoid, lepirudin, argatroban, or bivalirudin; ESC/ERS 2019 recommends fondaparinux if allergic or adverse reaction to LMWH.
g. ASH provides specific comments on the management of HIT in VTE in a dedicated guideline[18].

DOAC = direct oral anticoagulant; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; VKA = vitamin K antagonist; other abbreviations as in Figure 1.

in the early hours after PE diagnosis, closer monitoring of the adequacy of UFH may be considered. Although anti-Xa testing has been proposed as a preferred modality for UFH monitoring, consensus among evidence-based clinical practice guidelines is lacking and data supporting such a recommendation are limited.[37,38] Moderate-quality evidence demonstrates that fixed-dose low-molecular-weight-heparin (LMWH) is associated with a lower incidence of recurrent VTE and major hemorrhage compared with UFH.[39] Patients with low-risk PE, and those with intermediate-low-risk PE, can be treated with a DOAC from diagnosis, although dabigatran and edoxaban need a short course of initial heparin therapy [2,12,13] Parenteral direct thrombin inhibitors, such as argatroban or bivalirudin, can be used in place of UFH, while fondaparinux can be used in place of LMWH, in patients with a history of or suspected heparin-induced thrombocytopenia.[2,14,18] Oral anticoagulation with DOACs is recommended over vitamin K antagonists (VKAs), such as warfarin, except for patients with severe kidney disease with a creatinine clearance of <15 mL/min; those taking potent p-glycoprotein and/or CYP3A4 inducers or

inhibitors such as phenytoin, carbamazepine, or conazoles; and those with antiphospholipid syndrome.[2,12-14,16,20]

In patients with nongastrointestinal cancer and PE who do not require UFH, guidelines from CHEST[13] and NICE[20] recommend the use of a DOAC over LMWH. Conversely, ESC/ERS[2] and ASH[17] guidelines recommend either a DOAC or LMWH. Apixaban or LMWH may be the preferred option in patients with luminal GI malignancies according to the CHEST[13] guidelines. For initial anticoagulation in pregnant patients with PE, only the ESC/ERS guidelines[2] comment and suggest use of LMWH.

PRACTICAL CONSIDERATIONS. Anticoagulation therapy should be started while awaiting the results of confirmatory diagnostic testing if the pretest probability is intermediate or high, and the bleeding risk is low. Once the diagnosis of PE is confirmed, all patients without contraindications should receive anticoagulation. Those with low- and probably intermediate-low-risk PE can be treated with a DOAC. For patients with intermediate-high-risk PE, the guidelines do not provide detailed recommendations and there is heterogeneity in practice. The choice of UFH, LMWH, or a DOAC depends on local experience and case-specific considerations.

SUPPORTIVE CARE

Considering the limitations within the evidence base and the lack of a specific focus on this aspect, most guidelines are silent about details of supportive care. The 2019 ESC/ERS guidelines[2] provide general considerations on pharmacological supportive care. Modest fluid challenges are reasonable in patients with low central venous pressure, guided by invasive monitoring, ultrasound, or clinical monitoring. The use of furosemide in normotensive patients with intermediate-risk PE improves urine output but not early hemodynamic outcomes[40] and has not been discussed in the guidelines. Vasopressors, such as norepinephrine, can improve hemodynamics in shock, whereas the roles of dobutamine and levosimendan remain under review and are limited to specific conditions such as low cardiac index. Vasodilators, including inhaled nitric oxide and inhaled or intravenous prostanoids, may improve RV function especially in patients with signs of elevated pulmonary vascular resistance, but evidence supporting their safety and efficacy are lacking.[41] No formal recommendations concerning the use of pharmacological therapy for the supportive care of patients with high-risk PE are presented in any of the considered guidelines.

The decision to start supportive care with venoarterial extracorporeal membrane oxygenation should be based on local expertise, hemodynamic parameters, and an assessment of likelihood of long-term freedom from disability or complications.[42] Although the 2019 ESC/ERS guidelines[2] defined shock, the most recent CHEST[13] and ASH[16] guidelines did not. Unfortunately, a universal shock definition for acute PE is still lacking.

PRACTICAL CONSIDERATIONS. In the absence of consensus recommendations and rigorous clinical evidence, the selection of supportive care for patients with PE remains at the discretion of the clinician and local expertise and an important area of unmet research need.

ADVANCED THERAPIES

Although all referenced guidelines recommend reperfusion therapy as first-line for high-risk PE, the certainty (or level) of evidence supporting recommendations varies across documents.[2,12-14,16] Additionally, the heterogeneity in risk factors, pathophysiology, clinical presentation of VTE, and social determinants of health may modify the utilization of reperfusion therapy across populations.

According to all guidelines, patients with hemodynamically unstable PE, defined as a systolic blood pressure <90 mm Hg, or in cardiac arrest require rapid restoration of pulmonary perfusion and gas exchange as well as alleviation of increased RV afterload to prevent deterioration and death.[2,12-15] Although systemic fibrinolysis is recommended as the primary reperfusion therapy in high-risk PE,[2,12-14,16] the certainty (or level) of evidence supporting recommendations varies across documents (Supplemental Table 1). The primary evidence for systemic fibrinolysis for high-risk PE comes from a single randomized controlled trial (RCT) that enrolled 8 patients.[43] Additional evidence is derived from observational studies and epidemiological analyses. In clinical practice, systemic fibrinolysis remains underused in high-risk patients.[44] Although it has been hypothesized that reperfusion therapy may impact long-term outcomes, there is no current evidence supporting its use for preventing post-PE sequelae, including chronic thromboembolic pulmonary hypertension (CTEPH).[45] Surgical embolectomy remains an alternative to systemic fibrinolysis in centers with appropriate infrastructure, clinical staff, and procedural experience.[2,12,14] There is broad agreement among European and American guidelines with respect to avoiding routine administration of systemic fibrinolysis in intermediate-high risk (submassive) PE caused

FIGURE 4 Summary of Professional Society Recommendations for Advances Therapies in Acute PE

✓ Suggested ! Not Addressed ✗ Not Recommended	ESC/ERS[2]	PERT[12]	CHEST[13]	AHA[10,14]	ASH[16]	NICE[20]
Systemic fibrinolysis in hemodynamically unstable PE patients	✓	✓	✓	✓	✓	✓
Systemic fibrinolysis in hemodynamically stable experiencing hemodynamic and/or respiratory worsening	✓	✓	✓	✓	✓	✓
Reduced dose systemic fibrinolysis	✗	✓ b	!	!	!	!
Routine use of systemic fibrinolysis in hemodynamically stable PE patients	✗	✗	✗	✗	✗	✗
Surgical embolectomy in hemodynamically unstable PE patients	✓	✓	!	!	!	✓ e
CDIs in hemodynamically unstable PE patients in whom systemic fibrinolysis has failed or is contraindicated	✓	✓	✓	✓	✓ c	! f
CDIs in hemodynamically stable experiencing hemodynamic and/or respiratory worsening	✓	✓	✓	✓	! d	! f
Extracorporeal Membrane Oxygenation (ECMO)	✓ a	✓	!	!	!	!

a. ECMO may be considered in combination with surgical embolectomy or catheter-directed therapies in patients with refractory cardiogenic shock.
b. In high-risk patients with relative contraindications to systemic fibrinolysis.
c. In centers with the appropriate infrastructure, clinical staff, and procedural experience.
d. ASH prefers systemic fibrinolysis and endorses close cardiovascular monitoring to promptly identify the development of hemodynamic compromise.
e. Surgical thrombectomy may occasionally be performed for patients with a life-threatening PE.
f. Catheter-based embolectomy should only be used within the confines of research protocols due the absence of adequate supporting clinical trials.

CDI = catheter-directed intervention; ECMO = extracorporeal membrane oxygenation; other abbreviations as in Figure 1.

by the risk of major hemorrhage, especially intracranial bleeding.[2,10,12-14]

Over the past decade, catheter-directed interventions (CDIs) have generated growing interest for PE reperfusion in those with contraindications to systemic fibrinolysis (or after its failure).[10] These treatments can be classified into 2 main categories: catheter-directed fibrinolysis and catheter-based embolectomy.[46] All guidelines suggest the use of CDI, with different grades of recommendations, as rescue treatment after failure of systemic reperfusion or in individuals having a high bleeding risk.[2,12-14,16,20] However, there is no universal consensus regarding the use of CDI among different international guidelines, in large part caused by evidence gaps. Recently, the NICE[20] guidance stated that for intermediate- or high-risk PE, when alternative reperfusion treatments are suitable, catheter-based embolectomy should only be used within the confines of research protocols due the absence of adequate supporting clinical trials[21] (Figure 4). In patients with intermediate-high-risk PE, several ongoing randomized trials (NCT04790370, NCT05111613, NCT06055920, NCT05684796, NCT05591118) are investigating the efficacy and safety of CDIs in terms of early and long-term clinical outcomes. Randomized trials[47-49] and single-arm studies with hemodynamic outcomes have demonstrated that catheter-directed reperfusion techniques are associated with temporal improvement in RV dysfunction within 24 to 48 hours and reduced thrombus burden.[47-54] Available evidence comparing the safety and efficacy of CDIs with standard anticoagulation in intermediate-risk PE patients remains limited.

Notably, none of the current guidelines address the utility of advanced therapies to reduce long-term mortality, prevent persistent RV dysfunction, improve quality of life, and avert sequelae of post-PE syndrome and CTEPH.[45]

PRACTICAL CONSIDERATIONS. Systemic fibrinolysis remains the most widely recommended reperfusion technique to reduce mortality in high-risk PE. The

role of reperfusion and the optimal modality in intermediate-high risk PE remain unclear and are best addressed by a multitude of ongoing and forthcoming RCTs.

INFERIOR VENA CAVA FILTERS

Current best evidence derived from pooled results of prospective controlled studies across a heterogenous indications suggests that inferior vena cava (IVC) filter use, compared with nonuse, is associated with reduced risk of subsequent PE, at the expense of an increase in subsequent deep vein thrombosis, without a significant difference in mortality.[55] For patients with PE who can receive anticoagulant therapy, an RCT did not show additive benefit from the routine use of IVC filters.[56] The most widely agreed-upon indications for IVC filters across the guidelines are acute contraindication to systemic anticoagulation in patients with acute PE, and recurrent PE despite adequate administration and adjustment of anticoagulation. For several other clinical scenarios, there is marked heterogeneity across guidelines, in large part because of limited available high-quality evidence (Supplemental Figure 1).[2,12-14,16]

PRACTICAL CONSIDERATIONS. IVC filter use is recommended in patients with acute PE and a contraindication to anticoagulation or recurrent PE despite appropriate therapeutic anticoagulation.

FOLLOW-UP IMAGING AND CLINICAL ASSESSMENT

Appropriate follow-up after a PE diagnosis includes visits with routine health care workers and specialists, clinical examination, and noninvasive imaging. This long-term care is crucial to assess optimal recovery, the efficacy of anticoagulation, and potential bleeding complications as well as to evaluate for recurrent VTE events; potential PE-related complications, such as post-PE syndrome and CTEPH; and impact on quality of life.[2] Only the ESC/ERS[2] and the PERT[12] guidelines recommend a follow-up visit 3 to 6 months after discharge.

The ESC/ERS,[2] AHA,[14] and PERT[12] guidelines support the use of noninvasive imaging techniques, including TTE and, in selected cases, natriuretic peptides, and a 6-minute walk test[12] and/or cardiopulmonary exercise testing[2] to evaluate for the presence of pulmonary hypertension, especially in patients with persistent and otherwise unexplained dyspnea or impaired exercise tolerance 3 months after the acute event. V/Q scanning can be helpful to identifying mismatched perfusion defects.[2,12,14] Guidelines from the ESC/ERS,[2] PERT,[12] and AHA[14] suggest that symptomatic patients with pulmonary hypertension and/or mismatched perfusion defects should be evaluated at a referral center with experience in chronic thromboembolic disease, including CTEPH. Discussion of the management of post-PE syndrome is limited across the international guidelines (Supplemental Figure 2).

PRACTICAL CONSIDERATIONS. Although guideline recommendations are limited and many guidelines are silent on clear directives regarding how to monitor patients over time, clinical follow-up, including imaging, after acute PE serves several important purposes: to assess for recurrent events, to screen for bleeding complications, to identify potential post-PE sequelae, and to evaluate patients with persistent or new-onset dyspnea as well as signs of CTEPH. The routine use of follow-up CTPA or V/Q is not warranted. However, consideration of a follow-up TTE or V/Q scanning may be reasonable to further assess patients with residual symptoms or severe RV dysfunction, respectively.

LIFESTYLE MODIFICATIONS

Clinical practice guidelines and scientific statements on PE management remain largely silent on the role and relevance of lifestyle modification recommendations after PE[2,12-14,16,20] (**Figure 5**, Supplemental Figure 3). This is likely because of the lack of well-designed RCTs focusing on lifestyle modification. Nonetheless, lifestyle modification, such as smoking cessation and regular physical activity, may mitigate the increased risk of arterial cardiovascular disease as well as post-PE syndrome.[57] Despite the paucity of high-quality evidence specifically examining lifestyle modifications in the post-PE population, a recent clinical position paper by the ESC/ERS[58] proposed performance of a systematic cardiovascular risk assessment in PE survivors, and especially in those with unprovoked PE or with obesity, in accordance with other current guidelines for the general population.[58,59] The AHA Life's Essential 8 provides a comprehensive framework for focusing on key lifestyle modifications to improve cardiovascular health highlighting components of healthy diet, physical activity, avoidance of nicotine exposure, sleep health, maintenance of healthy body mass index and control of blood lipids, blood glucose, and blood pressure.[60] After acute PE, care should focus on lifestyle modifications aimed at fostering recovery and minimizing the risk of future cardiovascular

FIGURE 5 Summary of Post-PE Lifestyle Recommendations

Post-PE Lifestyle Recommendations

First Weeks	First Months	Long Term
Early Ambulation • Encourage early ambulation as soon as effective anticoagulation is achieved.[8]	**Post-PE Syndrome** • CTEPH evaluation and cardiopulmonary exercise testing in case of residual unexplained dyspnea.[4]	**Travel** • Counsel patients who discontinue anticoagulation about predictable major transient risk factors.[4]
Lifestyle Modification • Support patients toward a healthy lifestyle including adequate physical activity and smoking cessation.[4]	**Post-PE Syndrome** • Screen for anxiety or depression as contributors to incomplete recovery, refer to experts as needed.[4]	**Physical Activity** • Continue encouraging a healthy lifestyle including adequate physical activity.[4]
Physical Activity • Encourage stepwise resumption of sporting activities and screen for sexual dysfunction.[4]	**Cardiovascular Risk Factors** • General cardiovascular risk assessment and optimization, based on evidence-based guidelines.[4]	**Antithrombotic Regimen** • Review the use of antiplatelet agents. Most anticoagulated patients do not need them for stable atherosclerosis.[4]

Resumption of ambulation is recommended upon starting therapeutic anticoagulation,[72] with activities escalated as tolerated. Lifestyle modifications and cardiovascular risk optimization should be considered both initially and during follow-up visits. Early follow-up should assess symptoms of post-pulmonary embolism (PE) syndrome and consider testing exercise limitations as a sign of for chronic thromboembolic pulmonary hypertension, along with mental health screening. Long-term follow-up should counsel on prophylactic measures if anticoagulation is discontinued, and major surgery is upcoming. Most with stable atherosclerotic cardiovascular disease on anticoagulation likely do not need continued antiplatelet therapy.[57]

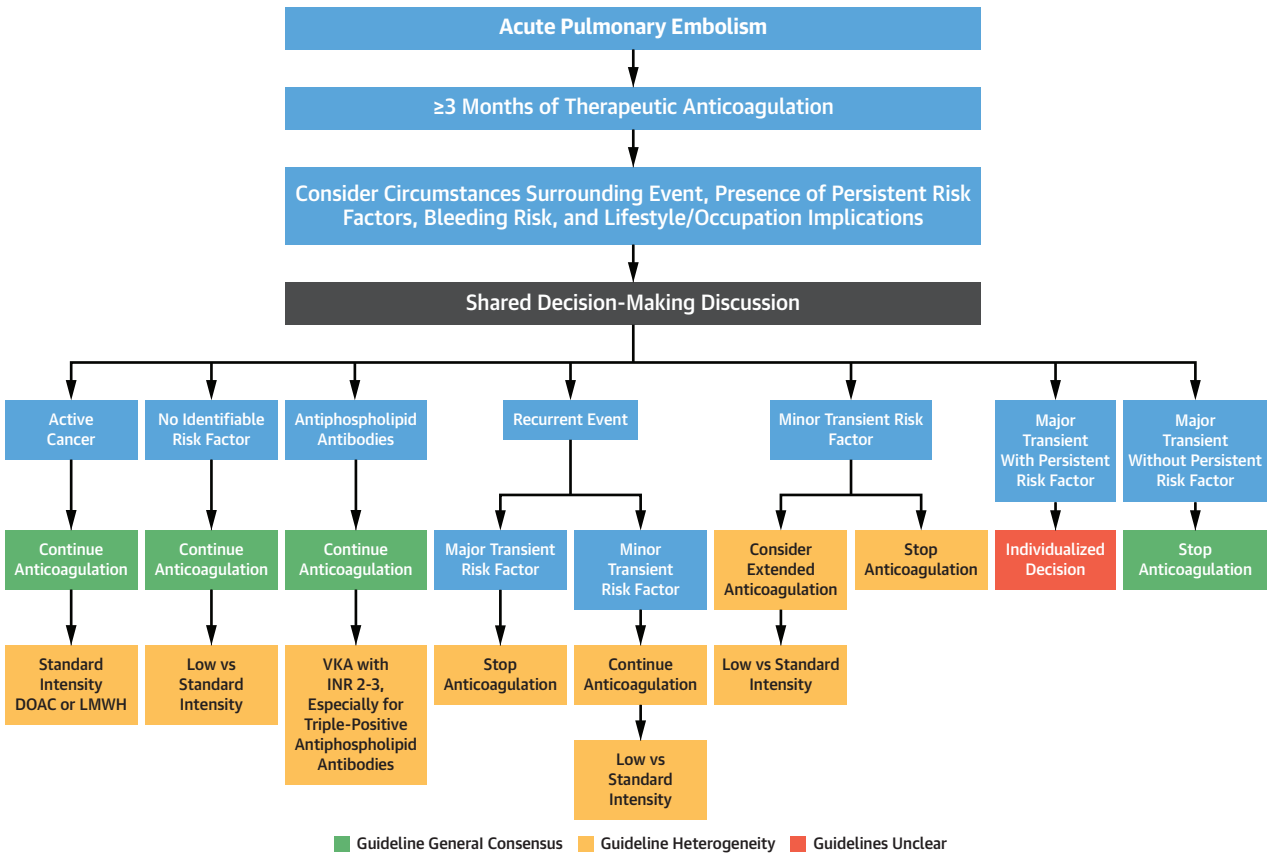
disease.[57] Cardiopulmonary exercise testing is suggested in selected cases after PE by the ESC/ERS guidelines.[2]

PRACTICAL CONSIDERATIONS. Although limitations in the evidence have resulted in relative silence among PE guidelines, lifestyle modifications, including smoking cessation, can be justified to mitigate risk factors for recurrent VTE and other cardiovascular complications.

INTENSITY AND DURATION OF ANTICOAGULATION

The International Society on Thrombosis and Haemostasis,[61] CHEST,[13] and ESC/ERS[2] guidelines provide insights into major and minor provoking factors for VTE, whereas the ESC/ERS[2] guidelines have classified patients into 3 distinct risk categories for long-term VTE recurrence: low, intermediate, and high risk. Patients with major transient or reversible risk factors (associated with a >10-fold increased risk of VTE), such as surgery under general anesthesia lasting for >30 minutes or experiencing immobilization for ≥3 days caused by acute illness or exacerbation of a chronic condition, are categorized as low risk, with an estimated VTE recurrence rate of <3% per year. Conversely, those with transient or reversible factors (associated with a ≤10-fold increased risk of VTE), including inflammatory bowel disease or active autoimmune disease, are placed in the intermediate-risk group, with a VTE recurrence risk estimated

FIGURE 6 International Guideline-Based Algorithm for Optimal Duration and Intensity of Anticoagulation for Pulmonary Embolism



INR = International Normalized Ratio; other abbreviations as in Figure 3.

between 3% per year and 8% per year. Finally, patients who have experienced PE and have active cancer, have had 1 or more previous episodes of VTE without major transient or reversible factors, or have antiphospholipid syndrome, are considered at high risk for VTE recurrence, with an estimated risk exceeding 8% per year.

The ESC/ERS,[2] ASH,[16] and CHEST[13] guidelines recommend at least 3 months of therapeutic anticoagulation for the primary treatment period unless there is a contraindication. Conversely, for secondary prevention or extended-duration therapy, guidance documents recommend considering the circumstances surrounding the incident event and the presence of persistent risk factors.[2,13,16,20] Guidelines that address the duration of anticoagulation are consistent in recommendations to discontinue anticoagulants in patients with PE provoked by major transient risk factors in the absence of enduring risk factors.[2,13,16,20] Likewise, guidelines recommend or suggest extended anticoagulation for patients with active cancer, and those with ongoing inflammatory disease or unprovoked PE (although with varying strength of recommendation). In contrast, guidance documents demonstrate heterogeneity in recommendations about the duration of anticoagulant therapy for PE provoked by minor transient risk factors. The NICE[20] and ASH[16] guidelines do not distinguish between major (eg, hospitalization, prolonged immobilization, surgery, and trauma) and minor transient risk factors (eg, oral contraceptives, pregnancy, and prolonged travel) and suggest that anticoagulation be discontinued after the primary treatment period. The ESC/ERS[2] guidelines recommend that extended anticoagulation beyond 3 months be considered in patients with persistent risk factors or those with PE in the setting of a minor transient risk factor.[2] Recommendations for this category are supported by lower grades of evidence and expert opinion and should be accompanied by

consideration of bleeding risk as part of shared decision-making. For recurrent PE in the setting of a transient provoking risk factor (ESC/ERS[2] guidelines qualify this as a major transient or reversible risk factor), only the ASH[16] guidelines specifically suggest stopping anticoagulation after primary treatment for the recurrent event. Outside of this setting, guidelines recommend or suggest continuing anticoagulation indefinitely for recurrent events.

Guidelines recommend that DOACs be preferentially used over VKA during both the primary treatment and secondary prevention periods.[2,13,16,20] For extended-duration treatment (secondary prevention), both the CHEST[13] and ESC/ERS[2] guidelines suggest a reduced dose (low-intensity)[62] of apixaban (2.5 mg twice daily) or rivaroxaban (10 mg once daily) over the standard full-dose treatment dose regimens. The ESC/ERS[2] and CHEST[13] guidelines suggest that this dose reduction be considered after at least 3 months of full-dose dose anticoagulation. The ASH guidelines suggest either a standard treatment dose or a low-intensity treatment in this phase.[16] Patients with antiphospholipid syndrome require indefinite oral anticoagulation with a VKA.[2,13,16,63] For treatment of PE in the setting of active cancer (persistent risk factor), guidelines recommend extending anticoagulation indefinitely or until there no longer evidence of malignant disease.[2,13,17] The ESC/ERS guidelines[2] recommend using weight-adjusted LMWH over a VKA or edoxaban or rivaroxaban in those with gastrointestinal cancer. Of note, those guidelines preceded the publication of results for apixaban in cancer-associated venous thrombosis.[64] The CHEST[13] and ASH[17] guidelines suggest apixaban, edoxaban, or rivaroxaban over LMWH or a VKA (**Figure 6**). Apixaban or LMWH may be the preferred option in patients with luminal GI malignancies according to the CHEST[13] guidelines.

PRACTICAL CONSIDERATIONS. Evidence-based guidelines recommend a minimum of 3 months of therapeutic anticoagulation after the diagnosis of PE. Beyond this acute treatment phase, recommendation of secondary prevention or extended-duration therapy should consider the presence of provoking circumstances, persistent conditions that predispose to recurrence, risk of bleeding, and lifestyle implications as part of a shared decision-making process. Except for specific patient populations, DOACs are preferred over VKAs for secondary prevention.

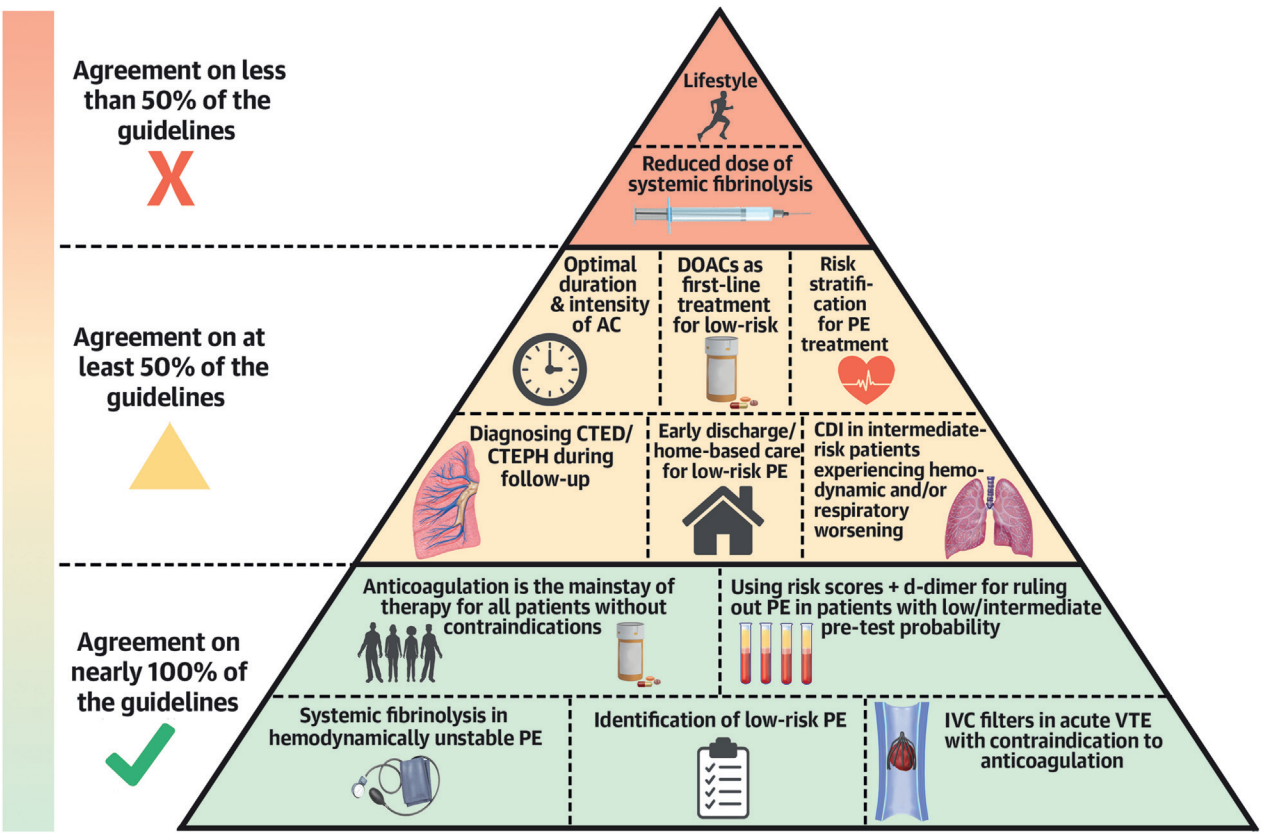
ADDITIONAL EVIDENCE/KNOWLEDGE GAPS

Notwithstanding the enormous progress that has been made over the past 4 decades, many critical questions related to prognostication, anticoagulation, and advanced management of PE remain unanswered, leading to heterogeneity in recommendations or silence in the existing guidelines (**Central Illustration**). The role of artificial intelligence in the timely and accurate diagnosis of PE remains to be seen. Innovation in risk stratification to synthesize the plethora of vital signs, clinical variables, and laboratory[33] and imaging biomarkers will be critical. Time-varying measures (such change in heart rate or hypoxemia) may assist in the identification of a preshock state.[50] Such detailed prognostication, paired with findings from several ongoing clinical trials and studies of laboratory or imaging markers, may identify subgroups that may benefit the most from specific interventions.[29,62,65] A more precise definition of the optimal therapeutic window for reperfusion may be needed, much like what has been done for patients with myocardial infarction.[66] Findings from clinical trials should also inform the minimal fibrinolytic doses required to achieve effective reperfusion and criteria for when to select nonfibrinolytic options.[66]

For clinical questions unlikely to have RCT data shortly, such as those related to the use of IVC filters and mechanical circulatory support, rigorous matched analyses from observational studies may be informative. Besides procedural therapies, findings from ongoing prospective studies and trials will be highly informative to determine the optimal duration and intensity of anticoagulation for patients with PE, including those with a first unprovoked PE, or those with provoked events who have enduring risk factors.[65,67] There is also an unmet need for high-quality comparative effectiveness studies focusing on the supportive care of high-risk PE or appropriate use of various advanced therapy options, particularly studies that incorporate the latest definitions of cardiogenic shock.[2,68,69] Similarly, additional high-quality studies are needed to better define the optimal therapeutic strategies in patients who are at risk but without clinically overt shock, such as those with preshock or normotensive shock and those with right heart thrombi or clot-in-transit.[50,70] Gaps in the published reports exist for patients who present outside of these larger categories such as those with PE and a major transient risk but with additional persistent risk factors and those with risk factors that are anticipated to improve over an extended period.[67]

Similarly, rigorous research is needed to define post-PE syndrome and to test strategies that may improve patient-centered outcomes in those who experience long-term non-CTEPH sequelae of PE. Social determinants of health and sex and ethnoracial differences require further investigation to

CENTRAL ILLUSTRATION **Consensus on Pulmonary Embolism Care Across U.S. and European Guidelines**


Agreement on less than 50% of the guidelines
X
Agreement on at least 50% of the guidelines
Agreement on nearly 100% of the guidelines
Lifestyle
Reduced dose of systemic fibrinolysis
Optimal duration & intensity of AC
DOACs as first-line treatment for low-risk
Risk stratification for PE treatment
Diagnosing CTED/ CTEPH during follow-up
Early discharge/ home-based care for low-risk PE
CDI in intermediate-risk patients experiencing hemodynamic and/or respiratory worsening
Anticoagulation is the mainstay of therapy for all patients without contraindications
Using risk scores + d-dimer for ruling out PE in patients with low/intermediate pre-test probability
Systemic fibrinolysis in hemodynamically unstable PE
Identification of low-risk PE
IVC filters in acute VTE with contraindication to anticoagulation

Zuin M, et al. JACC. 2024;84(16):1561–1577.

PE remains a major cardiovascular cause of mortality, despite clinical advancements. Clinicians encounter challenges in determining optimal anticoagulant strategies and interventions mainly because of the heterogeneity and uncertainty exhibited across numerous international guidelines. Among these guidelines, general agreement exists on most PE care recommendations, with variability in specifics. There is notable lack of consensus regarding lifestyle and usage of reduced dose of systemic fibrinolysis. AC = anticoagulation; CDI = catheter-directed intervention; CTED = chronic thromboembolic disease; CTEPH = chronic thromboembolic pulmonary hypertension; DOAC = direct oral anticoagulant; IVC = inferior vena cava; PE = pulmonary embolism; VTE = venous thromboembolism.

disentangle those related to biologically distinct pathways from those resulting from disparities that require population-level mitigation strategies.[9,71] Finally, RCTs are needed to help inform guidelines about the optimal lifestyle and dietary interventions to minimize the risk of incident PE, recurrent PE, and its adverse short-term or durable consequences (Supplemental Figure 4).

CONCLUSIONS

Evidence-based clinical practice guidelines for diagnosis and management of PE serve a critical role in summarizing state-of-the-art research and providing strategies for its integration in clinical care. However, guideline documents also provide an important mechanism for the identification of areas in the published reports for which data are inconsistent and associated recommendations are limited or conflicting. Harmonization of recommendations and research priorities across the various evidence-based clinical practice guidelines may ultimately represent a key step in reducing heterogeneity of care and improving patient and population outcomes.

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APPENDIX For a supplemental table and figures, please see the online version of this paper.

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